Chapter 2
The Changing Cigarette

Introduction

Cigarettes are the most common form of tobacco used in most of the world (World Health Organization [WHO] 2006) and cause 443,000 deaths in the United States each year (U.S. Department of Health and Human Services [USDHHS] 1986, 1988; National Cancer Institute [NCI] 1997; Centers for Disease Control and Prevention [CDC] 2008). The primary short- and long-range strategies for reducing deaths associated with tobacco use are cessation and prevention, respectively, along with reduction of secondhand smoke exposure (Warner et al. 1998; USDHHS 2000; Stratton et al. 2001; WHO 2003a). Another concept that has been considered is changing the cigarette itself to make it less toxic. The concept of modifying conventional cigarettes to be potentially less harmful is not new. Beginning in the 1950s, the tobacco industry embarked on efforts to modify cigarettes in response to growing public awareness of the health hazards of tobacco use, primarily through reducing machine-measured tar and nicotine content (NCI 1996). However, evidence now demonstrates that these modifications did not reduce the risk of cigarette smoking and in addition may have undermined efforts to prevent tobacco use and promote cessation (NCI 2001). In recent years, a range of new products have been introduced and marketed to smokers as an alternative to conventional cigarettes, sometimes accompanied by messages, explicit or implied, that they offer reduced exposure to toxic substances or risk of disease (Pederson and Nelson 2007). The focus of this chapter is on the health consequences of changes in cigarette design over time. Coverage of novel cigarette products is not intended to be comprehensive or current, because this market is rapidly evolving.

Cigarette Design Changes over the Years

The history of tobacco product design and marketing has been discussed elsewhere and need not be repeated (Reynolds and Shachtman 1989; Goodman 1993, 2004; Hilts 1996; Kluger 1996; Tate 1999; Brandt 2007). However, the tobacco industry's internal memoranda and other documents make it clear that the core concept and function of the cigarette has changed little since its invention in the early part of the nineteenth century; namely, it is a tobacco-derived product for delivering nicotine to the user (University of California at San Francisco [UCSF] 2008).

By the early 1950s, mounting scientific evidence began to implicate cigarette smoking in the development of serious respiratory, heart, and neoplastic diseases (Royal College of Physicians of London 1962; U.S. Department of Health, Education, and Welfare [USDHEW] 1964). This evidence created a new force in cigarette design that has remained prominent to this day: to design cigarettes that could be marketed as addressing the health concerns of both cigarette smokers and health professionals by reducing toxicants (Slade and Henningfield 1998; Stratton et al. 2001). Early efforts to reduce toxicants focused on efforts to reduce the overall tar (e.g., total particulate matter minus nicotine and water content) and nicotine yields of cigarettes.

The first major design change to reduce tar and nicotine yields was the introduction of filters in the 1950s. Before 1950, only 0.6 percent of cigarettes were filtered, but the increasing lay press coverage of the potential dangers of smoking led to an explosion of filter development and marketing. By 1960, filtered cigarettes represented 51 percent of the cigarette market (USDHHS 1989). By 2005, they represented 99 percent of the market. Major design efforts to reduce machine-measured tar and nicotine yields continued throughout the 1960s and 1970s with the introduction of "light" and low-tar cigarettes. Efforts to further reduce machine-measured tar and nicotine yields included the use of porous cigarette paper, reconstituted tobacco, filter tip ventilation, and the use of expanded tobacco (Hoffmann et al. 1996).

The initial focus on reduction of tar and nicotine yields was supported by early case-control studies suggesting that cancer risks were reduced by increased use of filters and decreased machine-measured tar delivery, and laboratory studies appeared to confirm this dose-response relationship. This research led to the seemingly reasonable conclusion that cigarettes with lower machine-measured tar and nicotine might pose fewer hazards, assuming that smokers did not increase the number of cigarettes they smoked per day or otherwise change their smoking behaviors (USDHEW 1967, 1969, 1971, 1974; USDHHS 1981; Stratton et al. 2001). Thus, it was widely accepted that declining tar and nicotine levels could lead to decreased disease risk. The concept that reduced exposure to

toxicants could reduce disease risk was supported by previous Surgeon General's reports (USDHEW 1969). In 1966, the U.S. Public Health Service recommended "the progressive reduction of the 'tar' and nicotine content of cigarette smoke" (USDHEW 1966, p. 2), and the Federal Trade Commission (FTC) announced that it would generally permit cigarette companies to make marketing claims about tar and nicotine yields as long as those statements were based on a uniform machine-based test method for measuring tar and nicotine yields, subsequently known as "the FTC method" (Peeler 1996; Pillsbury 1996).

Efforts to reduce tar and nicotine yields as measured on the basis of machine-smoking conditions were successful. The sales-weighted deliveries in U.S. cigarette smoke decreased from 38 milligrams (mg) of tar and 2.7 mg of nicotine in 1954 to 12 mg of tar and 0.95 mg of nicotine in 1993 (Hoffmann et al. 1996). Machine measurements of tar have shown little change since then, and machine measurements of nicotine delivery have remained at approximately 0.9 mg per cigarette since 1981 (*Federal Register* 1995, 1996; Slade et al. 1995; Hurt and Robertson 1998; Kessler 2001).

Unfortunately, with the accrual and evaluation of additional data, the evidence today does not demonstrate that efforts to lower machine-measured tar and nicotine yields actually decreased the health risks of smoking, primarily because these changes did not reduce smokers' actual exposure to tobacco toxicants (NCI 2001; USDHHS 2004). Indeed, to the extent that filters and other efforts to reduce machine-measured tar and nicotine reduced smokers' health concerns, and thereby delayed quitting and/or increased cigarette use, they may have contributed to an overall increase in cigarette-caused mortality (Stratton et al. 2001).

As mentioned above, for example, the first effort to change the design of cigarettes was the addition of the filter. In theory, use of filter technologies can remove substantial amounts of a wide variety of toxicants (Browne 1990; Hoffmann and Hoffmann 1997). In fact, however, evidence on the ability of filters to reduce harm is not clear (Slade 1993; NCI 2001; Stratton et al. 2001). And, some novel filter designs may introduce new toxicants such as asbestos (Slade 1993), carbon (Pauly et al. 1997), and glass (Pauly et al. 1998). The wide variation in filter technology across brands and over time precludes general conclusions about whether filters increased or decreased exposure of smokers to toxicants.

Similarly, a variety of design features made it possible for cigarette smokers to compensate, that is, easily ingest severalfold higher amounts of tar and nicotine than the yields obtained when using the machine-based FTC method (Djordjevic et al. 2000; NCI 2001; Stratton et al. 2001; WHO 2003c). Most important was the introduction of ventilation holes in the cigarette filters, which allowed smoke to escape during machine testing. In the 1980s, researchers discovered that smokers covered these ventilation holes with their fingers, negating the effect of the holes in reducing smoke exposure (Kozlowski et al. 1980, 2002, 2006). Moreover, subsequent research demonstrated that the use of ventilation holes produced higher levels of free-base nicotine, which led to a more addictive product as well as deeper lung inhalation of cooler and less harsh smoke (Stratton et al. 2001; Pankow et al. 2003a,b; Watson et al. 2004). Driven by nicotine addiction and enabled by cigarettes that delivered smoother, cooler smoke diluted by ambient air, smokers could easily compensate for reduced delivery of nicotine by increasing smoke intake per cigarette and per day, thus maintaining high levels of disease risk (NCI 2001; Thun and Burns 2001).

Tobacco industry documents, many of which are available at the Legacy Tobacco Documents Library at UCSF, clearly demonstrate that at least by the mid-1970s the tobacco industry well understood the importance of creating health reassurance messages in order to alleviate health concerns, and that one important method of doing so was through claims of low deliveries of tar. For example, a 1977 British American Tobacco marketing report concluded, "All work in this area should be directed towards providing *consumer reassurance* (*emphasis in original*) about cigarettes and the smoking habit. This can be provided in different ways, e.g. by claimed low deliveries, by the perception of low deliveries and by the perception of 'mildness'" (Short 1977, p. 3). At the same time, tobacco company documents also clearly demonstrate that the industry understood that smokers would not achieve the claimed deliveries because of smoker compensation. For example, a 1975 Philip Morris memo noted: "In effect, the Marlboro 85 smokers in this study did not achieve any reduction in smoke intake by smoking a cigarette (Marlboro Lights) normally considered lower in delivery" (Goodman 1975, p. 3).

In contrast to industry awareness, the various ways that cigarettes were physically modified and the nature and level of compensation in response to design changes were not well understood by parties outside of the tobacco industry itself. Public health officials had little basis to anticipate the degree to which manufacturers could design cigarettes to allow smokers to draw more smoke and nicotine from cigarettes than was represented by machine-measured yields of tar and nicotine (NCI 2001; Parascandola 2005).

It was not until the turn of the twenty-first century that it became increasingly clear that no relationship existed between machine-measured tar and nicotine levels and risks for most categories of cigarette-related diseases.

In 1994, an expert committee convened by NCI concluded: "The smoking of cigarettes with lower *machine-measured* yields has a small effect in reducing the risk of cancer caused by smoking, no effect on the risk of cardiovascular diseases, and an uncertain effect on the risk of pulmonary disease" (NCI 1996, p. vi). Moreover, whereas squamous cell carcinomas had been the predominant form of lung cancer, by the late twentieth century adenocarcinoma of the lung was becoming increasingly common, presumably reflecting deeper inhalation of smoke that was facilitated by ventilated filters as well as other factors such as changes in agricultural practices, tobacco curing, and cigarette manufacturing processes that could lead to increased concentrations of tobacco-specific nitrosamines (NCI 2001; Stratton et al. 2001) (see Chapter 5, "Cancer"). By 2001, NCI concluded that "measurements of tar and nicotine yields using the FTC method do not offer smokers meaningful information on the amount of tar and nicotine they will receive from a cigarette" (NCI 2001, p. 10). The 2001 review also concluded that the evidence "…does not indicate a benefit to public health from changes in cigarette design and manufacturing over the last fifty years" (NCI 2001, p. 10). Today, there is a scientific consensus that changes in cigarette designs from the 1950s to the 1980s to reduce machine-measured tar yields did not result in decreased morbidity and mortality (NCI 2001; Thun and Burns 2001). In sum, it took decades to recognize that changes to reduce machine-measured tar and nicotine yields in cigarettes did not have a measurable beneficial impact on public health (NCI 2001). In 2008, FTC rescinded its 1966 guidance that generally permitted statements concerning tar and nicotine yield if they were based on the Cambridge filter method (sometimes called the FTC method) (FTC 2008).

Other changes during the past 50 years have included efforts that potentially have made cigarettes more addicting through the use of flavors, chemical treatments to alter the smell and appearance of cigarette smoke, methods to mask noxious sensory effects, and control of the nicotine dose (see Chapter 4, "Nicotine Addiction: Past and Present"). These approaches included new types of filters, tobacco blends, and ingredients; cigarette ventilation; control of pH; and efforts to reduce various volatile organic compounds in tobacco and smoke. These product modifications have the potential to increase the risk of addiction by contributing to increased risk of initiating use of the product, increased ease of smoke inhalation, decreased noxiousness of the smoke, and possibly increased brain nicotine exposure (WHO 2007; Chapter 4, "Nicotine Addiction: Past and Present").

New Cigarette Products

Cigarette smoke contains more than 7,000 chemicals, including at least 69 known carcinogens and many other toxicants implicated in major diseases (International Agency for Research on Cancer [IARC] 2004; Borgerding and Klus 2005; Rodgman and Perfetti 2009), and because the potency of toxicants and mechanisms of action differ, reducing concentrations of individual toxicants might have only a negligible effect on disease risk from smoking (Fowles and Dybing 2003; Pankow et al. 2007; Burns et al. 2008). Despite these challenges, Brown & Williamson (acquired by R.J. Reynolds in 2004), Vector Tobacco, and Philip Morris have all developed cigarettes that purport to deliver lower levels of specific toxicants (e.g., carcinogenic nitrosamines) as determined by standard machine-smoking methods. This reduction in toxicant levels has been accomplished by use of new technologies in tobacco curing and/or by adding carbon or other materials to cigarette filters (Hoffmann et al. 2001; IARC 2004). However, the extent to which exposure to toxicants is actually reduced in smokers is not known because reduced machine-measured yields of toxicants do not necessarily reflect actual human exposure. A smoker who switches to a brand with lower machine-measured toxicants may smoke these cigarettes in a more intense fashion or may consume more cigarettes per day than previously. Either change could result in greater human exposure to toxicants and no decrease in risk of disease.

For example, Brown & Williamson introduced Advance as a new cigarette with the claim that levels of tobacco-specific nitrosamines (TSNAs) were 70 percent lower than those in leading "light" brands (Star Scientific 2005). Preliminary laboratory studies of cigarette smokers provide mixed evidence for the possibility that use of this cigarette substitute would result in reduced exposure to tobacco toxicants (Breland et al. 2002, 2003). Omni, manufactured by Vector Tobacco, is a conventional cigarette for which the marketers claimed lower levels of carcinogenic polycyclic aromatic hydrocarbons, nitrosamines, and catechols (Vector Group 2001). Preliminary studies in which Omni is smoked instead of the smokers' usual brand of cigarettes provide little evidence for reduced exposure to toxicants (Hatsukami et al. 2004b; Hughes et al. 2004).

Low-Nicotine Cigarettes

In theory, gradually reducing the content and yield of nicotine in cigarettes over a period of many years, using design features that make compensation difficult or impossible, might lessen smokers' dependence on nicotine. Low-nicotine cigarettes have also been proposed as a method to prevent new smokers (primarily youth) from ever establishing nicotine dependence (Benowitz and Henningfield 1994; Henningfield et al. 1998; Benowitz et al. 2007; Zeller et al. 2009). However, the potential role of nicotine analogues in maintaining addiction is poorly understood.

A commercial cigarette with very low nicotine content was introduced in test markets in 1989 under the brand name Next (Butschky et al. 1995). The nicotine content of Next appeared to be lower than the levels hypothesized by Benowitz and Henningfield (1994) to be the addictive threshold. The test market ended in 1991 when Philip Morris withdrew the product from the market. Quest was a low-nicotine cigarette developed by Vector Tobacco (Rose and Behm 2004; Vector Tobacco 2004). Three products were available: (1) a cigarette with 0.6 mg of nicotine and 10 mg of tar per cigarette, as determined by FTC machine measurements; (2) a cigarette with 0.3 mg of nicotine and 10 mg of tar per cigarette; and (3) a "nicotine-free" cigarette with no more than 0.05 mg of nicotine and 10 mg of tar per cigarette (Vector Tobacco 2004). It was unclear how long and how often smokers would use the "nicotine-free" version rather than versions that contained higher levels of nicotine and whether the two versions with nicotine would hinder the desire and ability to stop smoking.

Cigarette-Like Products

In 1988, R.J. Reynolds launched a new era of novel products with Premier, a nicotine-delivering product similar in size and appearance to a conventional cigarette but consisting of an aluminum canister that contained alumina beads impregnated with glycerin, propylene glycol, and a nicotine-rich tobacco extract (Slade 1993; Slade and Henningfield 1998). Heat from a carbon fuel element vaporized material adjacent to the alumina beads, and these vapors condensed into more proximal segments to form the aerosol that was puffed and inhaled by the consumer (Slade and Henningfield 1998). Compared with conventional cigarettes, Premier delivered similar doses of nicotine, higher levels of carbon monoxide (CO), and reduced levels of many other toxicants (WHO 2001). Premier was test marketed in the United States in 1988 but was soon withdrawn because of poor sales (Slade and Henningfield 1998).

More recently, tobacco companies have developed several other novel cigarette-like products that deliver nicotine to the consumer (Stratton et al. 2001; Slade et al. 2002). Eclipse (R.J. Reynolds) uses a technology similar to that developed for Premier (Slade and Henningfield 1998; Slade et al. 2002): the heat source is a carbon fuel element, and nicotine and glycerin are vaporized from an aluminum-lined chamber filled with what the manufacturer described as "highly processed tobacco" and mixed with glycerin. Both human and machine-testing data indicate that these products provide no clear benefit to users over conventional cigarettes. A report commissioned by the Commonwealth of Massachusetts Department of Public Health found that intensive machine smoking of Eclipse delivered levels of key lung and cancer-causing toxicants (e.g., acrolein, CO) similar to, or higher than, those from two commercial cigarette brands (Labstat 2000). A complication in evaluating the toxicity of Eclipse is that several prototypes were test marketed (Slade et al. 2002). It is not clear whether changes not disclosed by the manufacturer account for the variability across studies (Stapleton et al. 1998; Lee et al. 2004; Breland et al. 2006). Nonetheless, it appears that volunteers who had been exposed to Eclipse (Shiffman et al. 2004; Hughes et al. 2005) or had heard of it believed it to be less harmful than conventional cigarettes. Furthermore, concerns have been raised that Eclipse and Premier could be modified to deliver other drugs, including illicit drugs (Cone and Henningfield 1989; Steckley et al. 2002).

Accord (Philip Morris) consists of a specially designed "cigarette" used in combination with an ignition system (Slade and Henningfield 1998). The handheld, battery-operated, microchip-controlled product heats a cigarette-like tobacco roll when it is puffed (Slade and Henningfield 1998). Although actual-use studies of Accord have not been performed, preliminary laboratory studies with volunteers suggest the possibility that actual human exposure to nicotine and toxicants might substantially exceed that predicted by Philip Morris' tests (Buchhalter et al. 2001; Breland et al. 2002; Philip Morris USA 2005).

Evaluation of New Cigarette Products

The health consequences of new cigarette products have not been demonstrated in scientific studies. The challenges include a need for development and validation of testing methods for new products (WHO 2004b). Extended nonlaboratory studies under natural conditions with a broader range of biomarkers of toxicants are required to determine whether novel products result in overall reduction of exposure to toxicants, and still longer and more extensive studies would be required to determine whether or not the disease risk of the individual or population harm are decreased (WHO 2004a, 2007; Hatsukami et al. 2007). For example, products delivering lower levels of nitrosamines might theoretically reduce cancer risks, but because many of these products still deliver nicotine and CO, cardiovascular risks may remain unchanged or may even increase. In addition, if TSNAs are removed, other potent carcinogens may sustain overall high levels of exposure to carcinogens (Fowles and Dybing 2003).

There are substantial risks that the marketing of novel cigarettes could lead to increased tobacco use in current smokers, relapse in former smokers, and initiation in those who never smoked, particularly youth (Henningfield et al. 2003; Hatsukami et al. 2004a, 2005). For example, in a survey of 1,000 current cigarette smokers and 499 former smokers older than 18 years of age, 91 percent thought Eclipse was safer than regular cigarettes, 24 percent believed Eclipse was completely safe, and 57.4 percent were interested in using the product (Shiffman et al. 2004). Interest was greatest among those who were contemplating smoking cessation, and exposure to Eclipse's claims was followed by a reduced interest in cessation. Those interested in using Eclipse included 6.2 percent of all former smokers and 15.2 percent of young adults 18 through 25 years of age who had stopped smoking within the past two years. Further extending these findings, Hamilton and colleagues (2004) found that advertisements for light cigarettes were perceived to imply that their use is healthier than use of regular cigarettes, partly because consumers wrongly believed that the advertisements must be approved and endorsed by a government agency.

In addition, products designed or marketed to be used in places where smoking is not allowed may defeat public health efforts to reduce smoking rates. For example, studies have found that having a 100-percent smoke-free workplace reduced smoking prevalence by 6 to 22 percent and average daily consumption by up to 14 percent among smokers compared with workers subject to minimal or no restrictions (Farrelly et al. 1999; NCI 2000; USDHHS 2000; Bonnie et al. 2007). Products that enable nicotine consumption in the workplace and other places could reverse these potential reductions in smoking prevalence through use of one product in the workplace and continued smoking outside, that is, dual product use (Henningfield et al. 2002; European Commission 2007). Moreover, the dual use of tobacco products is likely to result in greater exposure to toxicants than does use of either product type alone (Henningfield et al. 2002).

Balancing the risks and benefits of new cigarette products is challenging because of the diversity of products, their associated potential risks and benefits on the multitude of tobacco-related diseases, and the dearth of empirical data on their effects. The 2001 Institute of Medicine (IOM) report (Stratton et al. 2001) and a report from the University of Minnesota Transdisciplinary Tobacco Use Research Center raised a series of questions about these and similar products (Hughes 2000; Stratton et al. 2001; Hatsukami and Hecht 2005; Hatsukami et al. 2005). WHO developed similar scientific questions, as well as recommendations for research and product testing (WHO 2003d, 2004a, 2006, 2007). Although all the questions raised by these organizations merit consideration, the following questions are a critical starting point for evaluating new cigarette or cigarette-like products:

- Does use of the product decrease individual and population exposure to the harmful substances in tobacco smoke?
- Is this decreased exposure associated with a decrease in individual and population risk of disease?
- Are there surrogate indicators of disease risk that could be measured in a timeframe of sufficient duration for product evaluation?
- What are the public health implications of products that may reduce exposure to toxicants in tobacco smoke? Specifically, do these products increase initiation of tobacco use, decrease cessation, promote relapse among those who have quit, or lead to dual product use?

New Oversight of Tobacco Products

On June 22, 2009, President Barack Obama signed into law the Family Smoking Prevention and Tobacco Control Act (Public Law 111-31). The Tobacco Control Act grants the U.S. Food and Drug Administration (FDA) the authority to regulate tobacco products to protect the public's health and recognizes FDA as the primary federal regulatory authority with respect to the manufacture, marketing, and distribution of tobacco products. Key elements of the act include, among other things, creation of a new Center for Tobacco Products, prohibition of the sale of cigarettes containing certain characterizing flavors, the requirement that manufacturers and importers report to FDA the ingredients and additives in their products, strengthened warning labels with graphic images of the adverse effects of cigarette use, and oversight of the tobacco industry's efforts to develop and market potential reduced-exposure tobacco products. The Tobacco Control Act also requires FDA to reissue the agency's 1996 regulation aimed at reducing young people's access to tobacco products and curbing the appeal of tobacco to the young. Although some provisions of the act went into effect shortly after the statute was enacted, such as the ban on flavored cigarettes, others will be implemented over time.

Sections 910 and 911 of the Tobacco Control Act provide that premarket review of certain tobacco products by FDA is required before the products may be marketed. Section 910 requires manufacturers of new tobacco products (those not commercially marketed as of February 15, 2007, or modified after that date) to submit an application containing specified manufacturing and ingredient information, as well as studies of the product's health risks, for FDA review. After reviewing the application, the agency will issue an order either permitting the product to be marketed or denying its marketing according to specified bases for its action. New tobacco products determined by FDA to be substantially equivalent to products already on the market as of February 15, 2007, are not required to undergo premarket review.

Section 911 provides that "modified risk tobacco products" may only be marketed if FDA determines, after reviewing a product application, that the product will significantly reduce the risk of tobacco-related disease to individual users, and benefit the health of the population as a whole, taking into account the impact on both users and nonusers of tobacco products. Section 911 recognizes so-called special rule products, which also require premarket approval. Such products may be marketed for up to five years (subject to renewal) if the agency determines that the applicant has met specified criteria, the applicant agrees to conduct certain postmarket surveillance and studies, and other specified findings regarding the relative harm of the product are made. Under this section, FDA must issue guidance or regulations on the scientific evidence required for the assessment and ongoing review of modified-risk tobacco products in consultation with IOM.

Summary

To reduce smoking-attributable death and disease, public health efforts since the 1964 Surgeon General's report on smoking and health have focused on reducing the prevalence of tobacco use. Reduced prevalence has been achieved through efforts to prevent tobacco use and promote cessation; this effort has been termed one of the "ten great public health achievements of the twentieth century" (CDC 1999). At the time the adverse effects of smoking were being recognized, the tobacco industry developed cigarettes with low machine-measured yields of tar and nicotine, and public health authorities encouraged consumers to select them (Peeler 1996; Shopland 2001). Unfortunately, it took public health researchers and federal authorities many years to discover what the tobacco industry knew much earlier: the health benefits of reductions of tar and nicotine intakes were negligible at best for persons using these products (*Federal Register* 1995, 1996; NCI 2001; WHO 2001; *U.S. v. Philip Morris* No. 449 F. Supp. 2d 1, 430–75 [D.D.C. 2006]). In 2001, an NCI report concluded: "There is no convincing evidence that changes in cigarette design between 1950 and the mid 1980s have resulted in an important decrease in the disease burden caused by cigarette use either for smokers as a group or for the entire population" (NCI 2001, p. 146). Thus, by the twenty-first century, it was apparent that five decades of evolving cigarette design had not reduced overall disease risk among smokers, and new designs were used by the tobacco industry as a tool to undermine prevention and cessation efforts (NCI 2001; Stratton et al. 2001; WHO 2001, 2003a,b,c; USDHHS 2004).

Similarly, informative and comprehensive scientific evaluations do not exist for any of the other new products developed ostensibly to reduce toxicants in cigarette smoke. This lack of data limits any conclusions that can be drawn about potential health risks or benefits.

The well-documented risks of cigarette design changes must be weighed against any potential benefits (Stratton et al. 2001). As this chapter makes clear, substantial risks may be associated with new tobacco products: (1) smokers who might have otherwise stopped smoking may continue to smoke because of perceived reduction in risk with use of new products; (2) former smokers may resume smoking because of perceived reduction in risk with use of new products; and (3) nonsmokers, particularly youth, may start to use new products because of their perceived safety. The theoretical benefit of cigarette design changes is to reduce exposure to toxicants sufficiently to reduce the risk of disease and death. However, if these products are used by persons otherwise unlikely to use a tobacco product, which would undermine efforts to prevent tobacco use, or if the products delay cessation among persons who would otherwise stop using tobacco, the overall health of the population would be harmed.

There is little doubt that new tobacco products will continue to be developed. Consequently, there is a critical need to conduct independent research on the design, composition, and health effects of new cigarette products and to put in place a comprehensive surveillance system to understand consumers' knowledge, attitudes, and behaviors regarding these products.

Conclusions

1. The evidence indicates that changing cigarette designs over the last five decades, including filtered, low-tar, and "light" variations, have not reduced overall disease risk among smokers and may have hindered prevention and cessation efforts.

2. There is insufficient evidence to determine whether novel tobacco products reduce individual and population health risks.

3. The overall health of the public could be harmed if the introduction of novel tobacco products encourages tobacco use among people who would otherwise be unlikely to use a tobacco product or delays cessation among persons who would otherwise quit using tobacco altogether.

References

Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P III. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(11):2479–85.

Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *New England Journal of Medicine* 1994; 331(2):123–5.

Bonnie RJ, Stratton K, Wallace RB, editors. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington: National Academies Press, 2007.

Borgerding M, Klus H. Analysis of complex mixtures—cigarette smoke. *Experimental and Toxicologic Pathology* 2005;57(Suppl 1):43–73.

Brandt AM. *The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product That Defined America*. New York: Basic Books, 2007.

Breland AB, Acosta MC, Eissenberg T. Tobacco specific nitrosamines and potential reduced exposure products for smokers: a preliminary evaluation of Advance. *Tobacco Control* 2003;12(3):317–21.

Breland AB, Buchhalter AR, Evans SE, Eissenberg T. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine & Tobacco Research* 2002;4(Suppl 2):S131–S140.

Breland AB, Kleykamp BA, Eissenberg T. Clinical laboratory evaluation of potential reduced exposure products for smokers. *Nicotine & Tobacco Research* 2006;8(6):727–38.

Browne CL. *The Design of Cigarettes*. 3rd ed. Charlotte (NC): Hoechst Celanese Corporation, 1990.

Buchhalter AR, Schrinel L, Eissenberg T. Withdrawal suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine & Tobacco Research* 2001;3(2):111–8.

Burns DM, Dybing E, Gray N, Hecht S, Anderson C, Sanner T, O'Connor R, Djordjevic M, Dresler C, Hainaut P, et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. *Tobacco Control* 2008;17(2):132–41.

Butschky MF, Bailey D, Henningfield JE, Pickworth WB. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacology, Biochemistry, and Behavior* 1995;50(1):91–6.

Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900–1999. *Morbidity and Mortality Weekly Report* 1999;48(12):241–3.

Centers for Disease Control and Prevention. Smoking attributable mortality, years of potential life lost, and productivity losses—United States, 2000–2004. *Morbidity and Mortality Weekly Report* 2008;57(45): 1226–8.

Cone EJ, Henningfield JE. Premier "smokeless cigarettes" can be used to deliver crack [letter]. *JAMA: the Journal of the American Medical Association* 1989;261(1):41.

Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *Journal of the National Cancer Institute* 2000;92(2): 106–11.

European Commission. Health Effects of Smokeless Tobacco Products Preliminary Report. Brussels: European Commission, Scientific Committee on Emerging and Newly Identified Health Risks, 2007; <http://ec.europa.eu/health/ph_risk/committees/04scenihr/docs/scenihr_o_009.pdf>.

Family Smoking Prevention and Tobacco Control Act, Public Law 111-31, *U.S. Statutes at Large* 123 (2009):1776

Farrelly MC, Evans WN, Sfekas AE. The impact of workplace smoking bans: results from a national survey. *Tobacco Control* 1999;8(3):272–7.

Federal Register. U.S. Department of Health and Human Services, Food and Drug Administration. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco products to protect children and adolescents; proposed rule analysis regarding FDA's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products; notice. 60 *Fed. Reg.* 41314–792 (1995).

Federal Register. U.S. Department of Health and Human Services, Food and Drug Administration. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents; final rule (21 CFR Parts 801, 803, 804, 807, 820, and 897). 61 *Fed. Reg*. 44396–5318 (1996).

Federal Trade Commission. FTC rescinds guidance from 1966 on statements concerning tar and nicotine yields [press release]. Washington: Federal Trade Commission, Office of Public Affairs, November 26, 2008.

Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tobacco Control* 2003;12(4):424–30.

Goodman B. Marlboro - Marlboro Lights study delivery data. 1975. Philip Morris Collection. Bates No. 2077992557. <http://legacy.library.ucsf.edu/tid/Awa18c00>.

Goodman J. *Tobacco in History: the Cultures of Dependence*. New York: Routledge, 1993.

Goodman J, editor in chief. *Tobacco in History and Culture: An Encyclopedia*. 2 Vol. Scribner Turning Points Library. Detroit: Charles Scribner's Sons, 2004.

Hamilton WL, Norton G, Ouellette TK, Rhodes WM, Kling R, Connolly GN. Smokers' responses to advertisements for regular and light cigarettes and potential reduced-exposure tobacco products. *Nicotine & Tobacco Research* 2004;6(Suppl 3):S353–S362.

Hatsukami D, Hecht S. *Hope or Hazard? What Research Tells Us about "Potentially Reduced Exposure" Tobacco Products*. Minneapolis: University of Minnesota Transdisciplinary Tobacco Use Research Center, 2005.

Hatsukami DK, Giovino GA, Eissenberg T, Clark PI, Lawrence D, Leischow S. Methods to assess potential reduced exposure products. *Nicotine & Tobacco Research* 2005;7(6):827–44.

Hatsukami DK, Henningfield JE, Kotlyar M. Harm reduction approaches to reducing tobacco-related mortality. *Annual Review of Public Health* 2004a;25:377–95.

Hatsukami DK, Joseph AM, Lesage M, Jensen J, Murphy SE, Pentel PR, Kotlyar M, Borgida E, Le C, Hecht SS. Developing the science base for reducing tobacco harm. *Nicotine & Tobacco Research* 2007;9(Suppl 4): S537–S553.

Hatsukami DK, Lemmonds C, Zhang Y, Murphy SE, Le C, Carmella SG, Hecht SS. Evaluation of carcinogen exposure in people who used "reduced exposure" tobacco products. *Journal of the National Cancer Institute* 2004b;96(11):844–52.

Henningfield JE, Benowitz NL, Slade J, Houston TP, Davis RM, Deitchman SD. Reducing the addictiveness of cigarettes. *Tobacco Control* 1998;7(3):281–93.

Henningfield JE, Moolchan ET, Zeller M. Regulatory strategies to reduce tobacco addiction in youth. *Tobacco Control* 2003;12(Suppl 1):i14–i24.

Henningfield JE, Rose CA, Giovino GA. Brave new world of tobacco disease prevention: promoting dual product use? *American Journal of Preventive Medicine* 2002;23(3):226–8.

Hilts PJ. *Smoke Screen: The Truth Behind the Tobacco Industry Cover-Up*. New York: Addison-Wesley Publishing Company, 1996.

Hoffmann D, Djordjevic MV, Brunnemann KD. Changes in Cigarette Design and Composition Over Time and How They Influence the Yields of Smoke Constituents. In: *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1996:15–37. NIH Publication No. 96-4028.

Hoffmann D, Hoffmann I. The changing cigarette, 1950–1995. *Journal of Toxicology and Environmental Health* 1997;50(4):307–64.

Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. *Chemical Research in Toxicology* 2001;14(7):767-90.

Hughes JR. Reduced smoking: an introduction and review of the evidence. *Addictio*n 2000;95(Suppl 1):S3–S7.

Hughes JR, Hecht SS, Carmella SG, Murphy SE, Callas P. Smoking behaviour and toxin exposure during six weeks use of a potential reduced exposure product: Omni. *Tobacco Control* 2004;13(2):175–9.

Hughes JR, Keely JP, Callas PW. Ever users versus never users of a "less risky" cigarette. *Psychology of Addictive Behaviors* 2005;19(4):439–42.

Hurt RD, Robertson CR. Prying open the door to the tobacco industry's secrets about nicotine: the Minnesota Tobacco Trial. *JAMA: the Journal of the American Medical Association* 1998;280(13):1173–81.

International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking*. Vol. 83. Lyon (France): International Agency for Research on Cancer, 2004.

Kessler D. *A Question of Intent: A Great American Battle with a Deadly Industry*. New York: Public Affairs, 2001.

Kluger R. *Ashes to Ashes: America's Hundred-Year Cigarette War, the Public Health, and the Unabashed Triumph of Philip Morris*. New York: Alfred A. Knopf, 1996.

Kozlowski LT, Frecker RC, Khouw V, Pope MA. The misuse of 'less-hazardous' cigarettes and its detection: hole blocking of ventilated filters. *American Journal of Public Health* 1980;70(11):1202–3.

Kozlowski LT, O'Connor RJ. Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. *Tobacco Control* 2002;11(Suppl 1):I40–I50.

Kozlowski LT, O'Connor RJ, Giovino GA, Whetzel CA, Pauly J, Cummings KM. Maximum yields might improve public health—if filter vents were banned: a lesson from the history of vented filters. *Tobacco Control* 2006;15(3):262–6.

Labstat International. Project Identifier: GC7 Labstat International Inc. Test Report. Prepared for the Commonwealth of Massachusetts, Department of Public Health. Kitchener (Canada): Labstat International. 2000. RJ Reynolds Collection. Bates No. 525005136/5153. http://legacy.library.ucsf.edu/tid/xqv27a00.

Lee EM, Malson JL, Moolchan ET, Pickworth WB. Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. *Nicotine & Tobacco Research* 2004;6(1):95–102.

National Cancer Institute. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1996. NIH Publication No. 96-4028.

National Cancer Institute. *Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control*. Smoking and Tobacco Control Monograph No. 8. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1997. NIH Publication No. 97-4213.

National Cancer Institute. *Population Based Smoking Cessation: Proceedings of a Conference on What Works to Influence Cessation in the General Population*. Smoking and Tobacco Control Monograph No. 12. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 2000. NIH Publication No. 00-4892.

National Cancer Institute. *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*. Smoking and Tobacco Control Monograph No. 13. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 2001. NIH Publication No. 02-5047.

Pankow JF, Barsanti KC, Peyton DH. Fraction of free-base nicotine in fresh smoke particulate matter from the Eclipse "cigarette" by 1H NMR spectroscopy. *Chemical Research in Toxicology* 2003a;16(1):23–7.

Pankow JF, Tavakoli AD, Luo W, Isabelle LM. Percent free base nicotine in the tobacco smoke particulate matter of selected commercial and reference cigarettes. *Chemical Research in Toxicology* 2003b;16(8):1014–8.

Pankow JF, Watanabe KH, Toccalino PL, Luo W, Austin DF. Calculated cancer risks for conventional and "potentially reduced exposure product" cigarettes. C*ancer Epidemiology, Biomarkers and Prevention* 2007;16(3):584–92.

Parascandola M. Lessons from the history of tobacco harm reduction: the National Cancer Institute's Smoking and Health Program and the "less hazardous cigarette." *Nicotine & Tobacco Research* 2005;7(5):779–89.

Pauly JL, Lee HJ, Hurley EL, Cummings KM, Lesses JD, Streck RJ. Glass fiber contamination of cigarette filters: an additional health risk to the smoker? *Cancer Epidemiology, Biomarkers & Prevention* 1998;7(11):967–79.

Pauly JL, Stegmeier SJ, Mayer AG, Lesses JD, Streck RJ. Release of carbon granules from cigarettes with charcoal filters. *Tobacco Control* 1997;6(1):33–40.

Pederson LL, Nelson DE. Literature review and summary of perceptions, attitudes, beliefs, and marketing of potentially reduced exposure products: communication implications. *Nicotine & Tobacco Research* 2007;9(5):525–34.

Peeler CL. Cigarette testing and the Federal Trade Commission: a historical overview. In: *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1996:1–8. NIH Publication No. 96-4028.

Philip Morris USA. Product facts: tar and nicotine numbers, 2005; <http://www.philipmorrisusa.com/en/product_facts/tar_nicotine/tar_nicotine_numbers.asp>; accessed: July 7, 2005.

Pillsbury HC. Review of the Federal Trade Commission Method for determining cigarette tar and nicotine yield. In: *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1996:9–14. NIH Publication No. 96-4028.

Reynolds P, Shachtman T. *The Gilded Leaf: Triumph, Tragedy, and Tobacco—Three Generations of the R. J. Reynolds Family and Fortune*. Boston: Little, Brown, 1989.

Rodgman A, Perfetti TA. *The Chemical Components of Tobacco and Tobacco Smoke*. Boca Raton (FL): CRC Press, Taylor & Francis Group, 2009.

Rose, JE, Behm FM. Effects of low nicotine content cigarettes on smoke intake. *Nicotine & Tobacco Research* 2004;6(2):309-19.

Royal College of Physicians. *Smoking and Health*. London: Pitman Medical Publishing, 1962.

Shiffman S, Pillitteri JL, Burton SL, Di Marino ME. Smoker and ex-smoker reactions to cigarettes claiming reduced risk. *Tobacco Control* 2004;13(1):78–84.

Shopland DR. Historical perspective: the low tar lie. *Tobacco Control* 2001;10(Suppl 1):i1–i3.

Short PL. Smoking and health item 7: the effect on marketing, April 28, 1977; <http://library.ucsf.edu/tobacco/batco/html/13300/13388/>; accessed: July 7, 2005.

Slade J. Nicotine delivery devices. In: Orleans CT, Slade J, editors. *Nicotine Addiction: Principles and Management*. New York: Oxford University Press, 1993:3–23.

Slade J, Bero LA, Hanauer P, Barnes DE, Glantz SA. Nicotine and addiction: the Brown & Williamson documents. *JAMA: the Journal of the American Medical Association* 1995;274(3):225–33.

Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? *Tobacco Control* 2002;11(Suppl 2): ii64–ii70.

Slade J, Henningfield JE. Tobacco product regulation: context and issues. *Food and Drug Law Journal* 1998;53(Suppl):43–74.

Stapleton JA, Russell MAH, Sutherland G, Feyerabend C. Nicotine availability from Eclipse tobacco-heating cigarette. *Psychopharmacology* 1998;139(3):288–90.

Star Scientific. Test marketed advance low tsna cigarette with dalmatian type activated charcoal/acetate filter: ADVANCE Onsert A; <http://www.starscientific.com/066745321909/OnsertA.html>; accessed: July 7, 2005.

Steckley SL, Darwin WD, Henningfield JE, Huestis MA, Pickworth WB. Eclipse can deliver crack cocaine. *Nicotine & Tobacco Research* 2002;4(Suppl 2):S189–S190.

Stratton K, Shetty P, Wallace R, Bondurant S, editors. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington: National Academy Press, 2001.

Tate C. *Cigarette Wars: The Triumph of the "Little White Slaver."* New York: Oxford University Press, 1999.

Thun MJ, Burns DM. Health impact of "reduced yield" cigarettes: a critical assessment of the epidemiological evidence. *Tobacco Control* 2001;10(Suppl 1):i4–i11.

U.S. v. Philip Morris, 449 F. Supp 2d 1 (D.D.C. 2006), *aff'd in part and vacated in part,* 566 F. 3d 1095 (D.C. Cir. 2009) *(per curiam), petitions for cert. filed,* Nos. 09–976 through 09–980, 09–994, 09–1012 (Feb. 19, 2010).

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1981. DHHS Publication No. (PHS) 81-50156.

U.S. Department of Health and Human Services. *The Health Consequences of Using Smokeless Tobacco. A Report of the Advisory Committee to the Surgeon General of the Public Health Service.* Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, 1986. NIH Publication No. (CDC) 86-2874.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General*. Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.

U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS Publication No. (CDC) 89-8411.

U.S. Department of Health and Human Services. *Reducing Tobacco Use. A Report of the Surgeon General*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2000.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.

U.S. Department of Health, Education, and Welfare. Technical Report on "Tar" and Nicotine. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service. 1966. Brown & Williamson Collection. Bates No. 680236352/6355. <http://legacy.library.ucsf.edu/tid/kaq04f00>.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking: A Public Service Review: 1967.* Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, 1967. PHS Publication No. 1696.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. 1969 Supplement to the 1967 Public Health Service Review*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, 1969. DHEW Publication No. 1696-2.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, 1971. DHEW Publication No. (HSM) 71-7513.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Report of the Surgeon General, 1974*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1974. DHEW Publication No. (CDC) 74-8704.

University of California at San Francisco. Tobacco Documents Bibliography, June 2008; <http://www.library.ucsf.edu/tobacco/docsbiblio.html>; accessed: September 15, 2008.

Vector Group. Reduced carcinogen cigarette now available; Vector Tobacco launches Omni nationwide [press release]. 2001. RJ Reynolds. Bates No. 528810104/0105. <http://legacy.library.ucsf.edu/tid/dyh93a00>.

Vector Tobacco. What is Quest? 2004; <http://www.vector-tobacco.com/prodInfo.asp>; accessed: July 7, 2005.

Warner KE, Peck CC, Woosley RL, Henningfield JE, Slade J. Tobacco dependence: innovative regulatory approaches to reduce death and disease [preface]. *Food and Drug Law Journal* 1998;53(Suppl):1–8.

Watson CH, Trommel JS, Ashley DL. Solid-phase microextraction-base approach to determine free-base nicotine in trapped mainstream cigarette smoke total particulate matter. *Journal of Agricultural and Food Chemistry* 2004;52(24):7240–5.

World Health Organization. *Advancing Knowledge on Regulating Tobacco Products*. Geneva: World Health Organization, 2001:47–55.

World Health Organization. Policy Recommendations for Smoking Cessation and Treatment of Tobacco Dependence. Geneva: World Health Organization, 2003a.

World Health Organization. *Recommendation on Health Claims Derived from ISO/FTC Method to Measure Cigarette Yield*. Geneva: World Health Organization, Scientific Advisory Committee on Tobacco Product Regulation, 2003b.

World Health Organization. *Recommendation on Nicotine and the Regulation in Tobacco and non-Tobacco Products*. Geneva: World Health Organization, Scientific Advisory Committee on Tobacco Product Regulation, 2003c.

World Health Organization. *Statement of Principles: Guiding the Evaluation of New or Modified Tobacco Products*. Geneva: World Health Organization, Scientific Advisory Committee on Tobacco Product Regulation, 2003d.

World Health Organization. *Guiding Principles for the Development of Tobacco Product Research and Testing Capacity and Proposed Protocols for the Initiation of Tobacco Product Testing*. Geneva: World Health Organization, Study Group on Tobacco Product Regulation, 2004a; <http://www.who.int/tobacco/global_interaction/tobreg/TobReg1finalfortfiweb.pdf>; accessed July 13, 2007.

World Health Organization. *Recommendations and Statement of Principles*. Geneva: World Health Organization, 2004b; <http://www.who.int/tobacco/sactob/recommendations/en/>; accessed: September 16, 2008.

World Health Organization. *Tobacco: Deadly in Any Form or Disguise*. Geneva: World Health Organization, 2006; <http://www.who.int/tobacco/communications/events/wntd/2006/Tfi_Rapport.pdf>; accessed: July 13, 2007.

World Health Organization. *The Scientific Basis of Tobacco Product Regulation. Report of a WHO Study Group*. Geneva: World Health Organization, 2007. WHO Technical Report Series No. 945.

Zeller M, Hatsukami D, Backinger C, Benowitz N, Biener L, Burns D, Clark P, Connolly G, Djordjevic M, Eissenberg T, et al. The strategic dialogue on tobacco harm reduction: a vision and blueprint for action in the United States. *Tobacco Control* 2009;doi:10.1136/tc.2008.027318.